APPARATUS AND METHOD FOR HEMODYNAMIC-BASED
OPTIMIZATION OF CARDIAC PACING

[0001] **CROSS REFERENCE TO RELATED APPLICATIONS**

[0002] The present invention claims the benefit of provisional U.S. patent application serial number 60/400,796 filed 2 August 2002 having common title hereof and the contents of which are hereby incorporated by reference herein.

[0003] The present invention relates to a non-provisional U.S. application serial number 10/629,075 now U.S. Pat. No. 7,027,866 entitled, "Mechanically-based Interval Optimization for a Biventricular Pacing Engine," invented by D. Warkentin, the contents of which are hereby incorporated by reference herein.

[0004] **FIELD OF THE INVENTION**

[0005] The present invention relates to the field of implantable medical devices. In particular, the present invention discloses apparatus and method for optimizing cardiac pacing algorithms based on hemodynamic physiologic data collected using a hemodynamic transducer implanted in a pacemaker patient. The present invention has specific utility with respect to heart failure patients suffering from related chronic symptoms.

[0006] **BACKGROUND OF THE INVENTION**

[0007] Cardiac resynchronization therapy (CRT) has gained increased use as an alternative treatment in patients with drug refractory heart failure and an intraventricular conduction delay. Current biventricular pacemakers offer a number of programmable parameters that have potential impact on the hemodynamic status, such as heart rate, AV- and VV-interval and pacing mode.

[0008] In patients with compromised central hemodynamics, optimization of pacemaker algorithms may be crucial for the treatment success of resynchronization. Echocardiography and Doppler techniques are commonly used to optimize the AV-delay based on measurements of the diastolic mitral inflow pattern or the aortic time velocity integral. However, echocardiography equipment is not

always easily accessible for the physician and the usefulness of a short-term evaluation of hemodynamic parameters at rest for long-term pacemaker programming in ambulatory patients is disputed. Therefore, an integrated hemodynamic sensor function may be helpful for the individual optimization of pacemaker devices used in patients with heart failure.

[0009]   Continuous hemodynamic monitoring with an implanted device is technically feasible, safe and delivers accurate measurements over time. Initial reports suggest that the monitor may help to tailor diuretic and other drug treatments in patients with chronic severe heart failure.

[0010]   The present invention is described with respect to a patient with end stage heart failure, implanted with both a biventricular pacemaker and a hemodynamic monitor. A prospective study was performed to evaluate if the hemodynamic monitor could be used for optimization of the AV-delay and heart rate.

[0011]   With respect to pressure sensing apparatus capable of chronic *in vivo* operation, many devices and methodologies have been proposed and/or implemented in the prior art. In this regard, the following issued U.S. patents provide added details for several representative pressure monitoring techniques; namely: U.S. Pat. Nos. 5,368,040; 5,564,434; 6,171,252; and 6,221,024 the contents of each are hereby incorporated herein as if fully set forth herein.

[0012]   **SUMMARY OF THE INVENTION**

[0013]   The present invention demonstrates that continuous hemodynamic monitoring can be used to identify the optimal AV-delay in a pacemaker-treated patient with end stage heart failure (HF). The AV-delay determines the timing of late diastolic filling in relation to the onset of ventricular contraction and the duration of diastolic filling. An optimal tuning of the AV-delay improves left ventricular filling pressures in patients with a DDD-programmed pacemaker and is particularly important in the presence of a compromised left ventricular function. It has been discovered that using the lowest estimated pulmonary artery diastolic pressure (ePAD), an indirect parameter of the left ventricular end-diastolic pressure, as an indicator for the optimal AV interval. Importantly,

measurements of the ePAD revealed the same optimal AV-delay as echocardiographic assessment of left ventricular diastolic filling by standard echocardiographic methods (Ritter).

[0014]   Importantly, the HR determined as optimal during the acute hemodynamic test did *not* turn out to be optimal during daily living in this patient. In the acute test a decrease of ePAD and RVDP was seen simultaneously with an increase of RVPP and maximal dP/dt at a heart rate of 90 bpm. The present invention demonstrates that continuous hemodynamic monitoring provides useful information for the optimization of hemodynamically important pacemaker algorithms such as the AV-delay, heart rate and pacing mode. In contrast to echocardiography, hemodynamic monitoring offers the potential to adjust pacemaker parameters even under the condition of exercise or during daily living. In patients with heart failure, the hemodynamic information may also be used to guide drug treatment and volume management.

[0015]   Therefore, future devices designed for the use in patients with heart failure, such as traditional dual chamber pacemakers, bi-ventricular resynchronization devices, ICDs, and the like may contain a hemodynamic monitoring sensor, constituting an integrated heart failure management device.

[0016]   **BRIEF DESCRIPTION OF THE DRAWINGS**

[0017]   FIG. 1 is a schematic diagram of a human heart showing the various chambers through which the blood flows as well as a pacing lead equipped with a right ventricular pressure sensor.

[0018]   FIG. 2 is a schematic diagram depicting a four channel, bi-atrial and bi-ventricular, pacing system in which the present invention is preferably implemented.

[0019]   FIG. 3 is a partially block, schematic diagram of a control system, responsive to a right ventricular pressure sensor signal, an ECG R-wave signal and an ECG P-wave signal.

[0020]   FIG. 4A illustrates a typical ECG signal.

[0021]   FIG. 4B illustrates a typical right ventricular pressure signal.

[0022]   FIG. 4C illustrates a signal derived from the derivative of the signal depicted in FIG. 4B, and which can be used to determine pulmonary artery systolic pressure as well as right atrial systolic and diastolic pressure.

[0023]   FIG. 4D illustrates a signal derived from the derivative of the signal depicted in FIG. 4C, and which can be used to determine pulmonary artery diastolic pressure.

[0024]   FIG. 5A illustrates an actual patient cardiac waveform of an ECG signal.

[0025]   FIG. 5B illustrates actual patient cardiac waveforms of pulmonary artery pressure and right ventricular pressure signals.

[0026]   FIG. 5C illustrates a waveform resulting from the derivative (dP/dt) of the right ventricular pressure signal depicted in FIG. 5C.

[0027]   FIG. 6 is a flow chart illustrating the steps of periodically determining the dP/dt_{max} and storing these data for use in adjusting one or more pacing delay intervals (e.g., A-V, A-A, V-V, PAV, SAV).

[0028]   Figure 7 depicts measured hemodynamic impact of different AV-delays during biventricular pacing at a heart rate of 70 bpm (mean and SD of 5 consecutive tests).

[0029]   Figure 8 is a table depicting various hemodynamic metrics for certain pacing intervals and heart rates.

[0030]   Figure 9 depicts continuous hemodynamic monitoring during 7 weeks at different back-up heart rates in a patient with a biventricular pacemaker. Median (dark line) 6th and 94th percentile (light line) of Right ventricular (RV) systolic pressure (RVSP) RV diastolic pressure (RVDP), RV pulse pressure (RVPP) and RV contraction velocity (RV dP/dt). The heart rate (HR) is represented by the dotted line.

[0031]   **DETAILED DESCRIPTION OF THE PRESENT INVENTION**

[0032]   The present invention was tested in the therapy for a 58 year-old male patient having cardiovascular risk factors that included cigarette smoking, hypertension and a family history of coronary artery disease and heart failure. In 1993 the patient suffered from an infero-lateral myocardial infarction (MI) that was treated by thrombolysis. Post infarction echocardiography revealed a moderately

enlarged left ventricle (LV) with a left ventricular ejection fraction (LVEF) of 45%. The patient underwent complete revascularization by coronary artery by-pass grafting (CABG) in August 1994. In the post surgery period the patient developed symptoms of severe heart failure and the LVEF decreased to 15-20%. Medical therapy with diuretics, enalapril, carvedilol, ASA, pravastatin and digoxin led to significant clinical improvement. In May 1999 the patient was included in a clinical trial conducted on behalf of Medtronic, Inc. of Minneapolis, Minnesota, U.S.A. (for the Chronicle® implantable hemodynamic monitor). This trial was a study to evaluate the technical accuracy and reliability of an implantable hemodynamic monitor (IHM) over time. Three months later, in August 1999, the patient had a minor stroke. The corresponding IHM information revealed an episode of paroxysmal atrial fibrillation (AF) and anticoagulant treatment with warfarin was started. During the following eight months the patient was hospitalized three times for a troponin positive acute coronary syndrome caused by paroxysmal AF. Each time the patient could be successfully cardioverted, but the patient's clinical status deteriorated steadily. In May, 2000 echocardiography measurements showed significantly enlarged ventricles with a left ventricular end-diastolic diameter (LVEDD) of 81 mm, LVEF of about 10%, mitral insufficiency (grade $^2/_4$) and tricuspid regurgitation (grade $^3/_4$). The patient was listed for heart transplantation.

[0033] Due to symptomatic bradycardia, first-degree heart block (P-Q interval of 260 ms) and a left anterior hemi-block with a QRS duration of 120 ms, a bi-ventricular pacemaker was implanted (the InSync® brand pacemaker manufactured by Medtronic, Inc.). The Chronicle® brand IHM (manufactuered by Medtronic, Inc. Model 9520) allows continuous, ambulatory hemodynamic recording using a pressure sensor placed in the right ventricular (RV) outflow tract. Heart rate (HR), activity and several pressure or pressure related parameters are measured and stored in the memory of the subcutaneously implanted device. The data collection can be programmed to various follow-up periods that regulate the storage interval. In this disclosure RV systolic pressure (RVSP), RV diastolic pressure (RVDP), estimated pulmonary artery diastolic (ePAD) pressure (10,11), rate-of-change pressure (dP/dt) and HR

measured both acutely (storage interval of two seconds) and ambulatory (storage interval of six minutes) are described.

[0034]   Hemodynamic information from the IHM was collected at rest during test protocols including eight paced AV (PAV) intervals (110-250 ms) and seven different HR (50-110 bpm). AV-intervals were always tested at a HR of 70 bpm and HR at an AV-delay of 180 ms (paced) and 130 ms (sensed). The different AV-intervals and HR were programmed in a randomized order for 1-2 minutes each and a median of the last 30 seconds was used for the data analysis. The protocol was repeated each week over five consecutive weeks. Echo-Doppler measurements were used to assess the diastolic mitral inflow pattern. According to the Ritter method of echocardiography, the AV-delay providing complete end-diastolic filling without shortening of the diastolic filling time was considered optimal. In addition the hemodynamic impact of four different heart rates (60-90 bpm) were tested during periods of 5-14 days each while the patient was at home performing activities of daily living (ADL).

[0035]   Turning now to the drawings, FIG. 1 provides a schematic cross-sectional diagram of a human heart 10 from which an understanding of hemodynamic pumping action can be derived. With this background, a better understanding of abnormal cardiac pumping actions, such as CHF and LVD may be gained. A human heart 10 has an intrachamber septum 64 dividing the cardiac chambers on the left side (LA,LV) from the right side (RA,RV). The two atrial chambers 40,52 each have a valve that allows blood to pass through to the ventricles. The tricuspid valve 42 and mitral valve 54 regulate blood flow between the atrium and the ventricle on each side. As described, when RV pressure reaches a maximum positive rate-of-change pulmonary valve 46 opens to allow venous blood to flow from the RV to the pulmonary arteries 48,50 which supply blood to the lungs. Aortic valve 58 regulates blood flow from the left ventricle to aorta 60 and to the body.

[0036]   The circulation of the blood through heart 10 begins on the right side (left side of drawing). Relatively large veins, the superior vena cava and inferior vena cava (not shown) return blood from the body to right atrium 40. This blood then flows through tricuspid valve 42 into right ventricle 44, and leaves right ventricle 44

through pulmonary valve 46 then to the lungs via right 48 and left 50 pulmonary arteries. The two arterial branches carry blood to the right and left lungs (not shown). Oxygenated blood from the lungs reenters the heart 10 flowing into left atrium 52 and passes into left ventricle 56 through mitral valve 54. The blood leaves left ventricle 56 through the aortic valve 58 to enter aorta 60. According to the present invention, a pressure sensor 62 couples to a right ventricular pacing lead 64.

[0037]   The hemodynamic, or pumping, action of the heart 10 depends almost totally on changes or differences in pressure gradients between the heart's chambers. Cardiac output, the volume of blood ejected from each ventricle during one minute, is the product of heart rate, ejection fraction and stroke volume. Stroke volume is the volume of blood ejected with each heartbeat and depends on preload, myocardial contractility and afterload. Preload refers to the load that stretches the cardiac muscle prior to contraction. The amount of blood in the right ventricle at the end of diastole constitutes preload for the next beat. Right ventricular preload is altered by increasing venous return to the right heart as seen with inspiration and exercise. Conversely, dilated capillary beds and exhalation will decrease venous return. Afterload refers to the resistance against which the ventricle must contract. Resistance can be the result of: thickness and flexibility of the walls of the aorta and large arteries, the peripheral vascular tree, volume of the blood and the viscosity of the blood, among others.

[0038]   Myocardial contractility is the ability of the cardiac muscle to shorten when given a load. Contractility can be increased by the action of the sympathetic nervous system and decreases when the myocardium is damaged. Because of the way the heart depolarizes, events on the left side of the heart typically slightly precede events on the right side. Thus, the mitral valve 54 closes slightly ahead of the tricuspid valve 42 and the aortic valve closes slightly ahead of the pulmonic valve. The staggered closing of the valves produces a splitting of the S_1 and S_2 heart sounds. Splitting of the second heart sound is exaggerated by inspiration due to the pressure drop in the thoracic cavity. Respiration has little effect on S_1 splitting. Normally ventricular systole is slightly shorter than

diastole. As heart rate increases, the difference in duration decreases. At about 120 beats per minute, the phase lengthens and becomes nearly equal.

[0039]   Several disorders of the heart have been studied which prevent the heart from operating normally. One such disorder is from degeneration of the LV conduction system, which blocks the propagation of electric signals through some or all of the fast conducting Purkinje fiber network. Portions of the LV that do not receive electrical signals through the fast conducting Purkinje fiber network can only be depolarized through muscle tissue conduction, which is slow and occurs in sequential manner. As a result, the contraction of these portions of the LV occur in stages, rather than synchronously. For example, if the posterior wall of the LV is affected by the conduction disorder, then it contracts later than the septum that is activated through normal conduction. Such asynchronous contraction of the LV walls degrades the contractility (pumping power) of the LV and reduces the LV dp/dt_{max}.

[0040]   If a heart failure patient suffers from another affliction, such as dilated cardiomyopathy (DCM), in addition to conduction disorder(s), hemodynamic inefficiency will likely render the patient symptomatic.

[0041]   Another disorder of the heart occurs when blood in the LV flows back into the LA, resulting in reduced stroke volume and cardiac output. This disorder is called mitral regurgitation and can be caused by an insufficiency of the mitral valve, a dilated heart chamber (due to DCM), or an abnormal relationship between LV pressure and LA pressure. The amount of the back flow is a complex function of the condition of the mitral valve, the pressure in the LV and in the LA, and the rate of blood flow through the left heart.

[0042]   These disorders may be found separately or in combination in patients. For example, such disorders are found in patients exhibiting congestive heart failure (CHF). CHF is a disorder of the cardiovascular system. Generally, CHF refers to a cardiovascular condition in which abnormal circulatory congestion exists as a result of inadequate blood flow. Circulatory congestion is a state in which there is an increase in blood volume in the heart but a decrease in the stroke volume. Reduced cardiac output could be due to several disorders, including mitral regurgitation (a back flow of blood from the LV to the LA) and intrinsic

ventricular conduction disorder (asynchronous contraction of the ventricular muscle cells), which are the two common abnormalities among CHF patients.

[0043] When delivering CRT to a patient, it is important to synchronize the systolic contractions of both the right and left sides of the heart. A useful physiologic measurement for ascertaining such synchronized systolic function is fluid pressure developed during delivery of CRT to the patient. As noted herein, measuring pressure developed at discrete moments during a cardiac cycle provides a strong indication of synchronization. The present invention provides for use of direct measurement of RV pressure, derivatives thereof (e.g., $dP/dt_{max/min}$), and, assuming that computational overhead and current drain is not too great, integrals thereof.

[0044] PA diastolic pressure is similarly determined from the RV. As long as the PA pressure is higher than the RV pressure, the PA valve is closed. As the ventricle begins to contract during systole, however, the RV pressure surpasses the PA pressure and the PA valve opens. Thus, the pressure in the PA at the time the PA valve opens is the lowest pressure seen by the pulmonary artery and, therefore, corresponds to PA diastolic pressure. Accordingly, the PA diastolic pressure is the pressure in the RV at the moment the PA valve opens. When the PA valve opens has been shown to be nearly identical to the time of maximal positive rate-of-change increase in RV pressure (i.e., dP/dt_{max}). The point of dP/dt_{max} is when the PA valve is open and the pressures are equal between the PA and RV and correlates to the so-called estimated pulmonary artery diastolic (ePAD) pressure. Furthermore, pulse pressure (PP) measurements, both direct and via a suitable pressure surrogate, provides an excellent metric upon which hemodynamic optimization may be based.

[0045] FIG. 2 is a schematic representation of an implanted, three channel (or triple chamber) cardiac pacemaker for restoring synchronous contractions to the atrial and ventricular chambers while also providing simultaneous or sequential pacing to both ventricles. Implantable pulse generator (IPG) 14 is implanted subcutaneously in a patient's body between the skin and the ribs. Three endocardial leads 16, 32 and 72 connect the IPG 14 with the RA, the RV and the LV, respectively, through connections made in the IPG connector block 12. A remote indifferent electrode may be formed as part of the outer surface of housing 20 of IPG 14.

[0046] The present invention will be described herein in an embodiment that includes an IPG configured to deliver CRT. Those of ordinary skill in the art, however, with the benefit of the present disclosure will appreciate that the present invention may be advantageously practiced in connection with numerous other types of IMDs such as defibrillators, cardioverters, and the like.

[0047] The depicted bipolar endocardial RA lead 16 is passed through a vein into the RA, and the distal end of RA lead 16 is implanted in the RA appendage or fixed to the RA wall by a positive fixation

mechanism 17. Bipolar endocardial RA lead 16 is connected via an in-line connector 13 fitting into connector block 12 that is coupled to a pair of electrically insulated conductors within lead body 15 and connected to distal tip RA pace/sense electrode 19 and proximal ring RA pace/sense electrode 21. Delivery of atrial pace pulses and sensing of atrial sense events typically occurs between the distal tip RA pace/sense electrode 19 and proximal ring RA pace/sense electrode 21, wherein the proximal ring RA pace/sense electrode 21 functions as an indifferent electrode. Alternatively, a unipolar endocardial RA lead could be substituted for the depicted bipolar endocardial RA lead 16 so that sensing occurs between a unipolar RA lead and the (indifferent electrode) housing 20 of IMD 14. Bipolar, endocardial RV lead 32 is passed through a vein and the RA chamber of heart 10 and into the RV where its distal ring and tip RV pace/sense electrodes 38,80 may be disposed in the apex of the RV by a conventional distal attachment mechanism 81. The RV lead 32 is electrically and mechanically coupled via an in-line connector 34 into a bipolar bore of connector block 12 that is coupled to a pair of electrically insulated conductors within lead body 36 and connected with distal tip RV pace/sense electrode 80 and proximal ring RV pace/sense electrode 38.

[0048]   In this illustrated embodiment, a bipolar, endocardial coronary sinus (CS) lead 72 is passed through a vein and the RA chamber of the heart 10, into the CS and then inferiorly into a branching vessel of the great vein (GV) to extend the proximal and distal LV CS pace/sense electrodes 78 and 70 alongside the LV chamber. The distal end of such a CS lead is advanced through the superior vena cava, the right atrium, the ostium of the coronary sinus, the coronary sinus (CS), and into a left descending coronary vein, such as the GV.

[0049]   In a four chamber pacemaker (4CP) embodiment, LV CS lead 52 could bear proximal LA CS pace/sense electrodes 28 and 30 positioned along the CS lead body to lie in the larger diameter CS adjacent the LA. Typically, LV CS leads and LA CS leads do not employ any fixation mechanism and instead rely on the close confinement within these vessels to maintain the pace/sense electrode or electrodes at a desired site. The LV CS lead 72 is formed with a multiple conductor lead body 76 coupled at the proximal end connector 74 fitting into a bore of IPG connector block 12. A small diameter lead body 76 is selected in order to lodge the distal LV CS pace/sense electrode 70 deeply in a vein branching inferiorly from the great vein (GV).

[0050]   In this case, the CS lead body 56 would encase four electrically insulated lead conductors extending proximally from the more proximal LA CS pace/sense electrode(s) and terminating in a dual bipolar connector 74. The LV CS lead body would be smaller between the LA CS pace/sense electrodes 28 and 30 and the LV CS pace/sense electrodes 78 and 70.

[0051]   Turning now to FIG. 3, there is depicted one embodiment of a pressure sensing circuit 11 that operatively couples to pacing circuitry resident in the IMD 14 illustrated in FIG. 2 and that is used for determining the hemodynamic status of

a patient. It is to be understood that IMD 14 is contained within a hermetically-sealed, biologically inert outer shield or "can", in accordance with common practice in the art. The sensing circuit 11 is operable in conjunction with an implantable absolute pressure sensor 62 that is implanted in the patient's RV as depicted in FIG. 1 and couples pressure signal 412 to pressure sensing circuit 11. The IMD 14 includes pressure sensing circuit 11 as well as other circuitry as is well known to those of skill in the art.

[0052]   Operation of the implantable medical device 14 will now be discussed in more detail with reference to FIGS. 4 and 5. As stated above, measurements of pressure developed, particularly pulmonary wedge pressure, inside the heart are typically used to determine the health of a patient and provide a proper therapy. One illustrative method for determining pulmonary artery and right arterial diastolic and systolic pressure begins with reference to the simplified block diagram of pressure sensing circuit 11 illustrated in FIG. 3. The basic functional components are differentiators 340,342, comparators 336,338,344, sample-and-holds 332,334,346,350, and delays 330,348. Embodiment 11 also requires the output 314 from an R-wave sense amplifier and the output 316 from a P-wave sense amplifier, as known to those skilled in the art of cardiac pacing. Thus, the timing of the delivered cardiac stimulation and evoked (or intrinsic) response can readily be linked to developing pressure as measured by pressure sensing circuit 11 and as provided via signal 412.

[0053]   Operation of embodiment 11 shown in FIG. 3 begins by differentiating the signal 412 from an absolute pressure sensor 62 (FIG. 1) which is chronically implanted in the RV, to provide a first and a second derivative of the RV pressure signal (i.e., dP/dt and d^2P/dt^2 respectively). A typical ECG signal is illustrated in FIG. 4A while its associated right ventricular (RV) pressure sensor waveform 412 is shown in FIG. 4B. Differentiator 340 provides an output signal 402 illustrated in FIG. 4C that is the first derivative of waveform 412. Differentiator 342 provides an output signal 404 illustrated in FIG. 4D that is the second derivative of waveform 412. From these waveforms (and relates mathematical derivations) the PA diastolic pressure and PA systolic pressure are readily obtained. That is, as previously described PA diastolic pressure occurs when maximum

positive rate-of-change of RV pressure occurs (upon opening of PA valve) and, PA systolic pressure occurs at maximum RV pressure (while the PA valve is still open).

[0054]   FIG. 4A depicts a representative cardiac surface ECG waveform for a single cardiac cycle. The ECG reveals a P-wave 402 and an R-wave 404 that forms a portion of the QRS complex as well as a T-wave and a U-wave. Like other drawings contained herein, FIG. 4A is not rendered to scale; however, FIG. 4A more or less accurately represents a cardiac cycle during normal sinus rhythm (NSR) although the present invention is not limited to operation only during NSR. Inspection of the waveforms shown in FIGS. 4b-4D, which represent a waveform 412 from a direct measurement of RV pressure, a first derivative 402 of the RV pressure waveform 412, and a second derivative 404 of said RV pressure waveform 412, respectfully, it can be seen that the maximum RV (and PA) systolic pressure occurs the first time after the R-wave 406 that the first derivative waveform (dP/dt) 402 passes through zero (i.e., has a null value). It follows from the discussion above that the maximum dP/dt (corresponding to PA diastolic pressure) occurs when the waveform representing the first derivative 402 has a maximum positive value. This also corresponds to the first time after the R-wave 406 that the waveform representing the second derivative 404 transitions from a positive value to a negative value (i.e., has a null value).

[0055]   With reference to FIGS. 5A to 5C, these three drawings depict a temporal sequence of ventricular stimulation (VEGM 502) showing an R-wave evoked at 504 due to ventricular pacing stimulation, FIG. 5B depicts two waveform traces namely PA pressure 518 and RV pressure 412, and FIG. 5C depicts a waveform 506 representing the first derivative of the RV pressure 412 of FIG. 5B. In FIG. 5B, the PA diastolic pressure (i.e., ePAD) waveform is identified as aligned with the occurrence of maximum positive rate-of change of the RV pressure (i.e., dP/dt_{max}). Also depicted in FIG. 5B is the PA systolic pressure that corresponds to a null value of the first derivative of RV pressure and also corresponds to the maximum negative value of the second derivative of RV pressure (see e.g., FIG. 5C). Also depicted in FIG. 5C, the right atrial (RA) systolic pressure can be seen to align with a null value for the first derivative of

the RV pressure signal that occurs prior to the occurrence of dP/dt$_{max}$. With reference again to FIG. 5B, representative waveforms of developing pulmonary artery (PA) pressure and right ventricular (RV) pressure are illustrated. From FIG. 5B it is readily apparent that PA diastolic pressure (minimum PA pressure) occurs at essentially the same moment when the PA pressure and RV pressure signals cross each other (i.e., when the PA valve opens during the maximum rate-of-change of RV pressure).

[0056]   FIG. 5C is the dP/dt waveform 506 resulting from a first derivative of the patient's RV pressure signal 412. Again, note that the maximum positive amplitude of the dP/dt waveform 506 occurs at the same time that the PA pressure 518 equals the RV pressure 412. Also illustrated in FIG. 5C is that PA systolic pressure occurs at the approximate time that the first derivative equals a null value (corresponding to the top of the peak of an RV pressure waveform 412).

[0057]   Referring again to the simplified circuit diagram of pressure sensing circuit 11 depicted in FIG. 3 (and with reference to FIGS. 4A-4D), the PA systolic pressure 322 is determined by feeding the RV pressure sensor output 412 into a sample and hold circuit 334. The sample and hold circuit 334 is triggered by the sensing of the R-wave 406 shown in FIG. 4A. The systolic pressure 322 is then latched when the dP/dt waveform 402 illustrated in FIG. 4C goes negative (i.e., achieves a null value) as determined by comparator 336 output signal 328. This value of systolic pressure will be held until the next R-wave 406 is sensed, enabling the sample and hold circuit 334 to change values. Of course, a series of systolic pressure values may be read from the sample and hold circuit 334 and stored in an available memory location for later comparison or manual review in the context of the then-present operative pacing intervals. Similarly, the PA diastolic pressure is determined by feeding the RV pressure signal 412 into a sample and hold circuit 332 which is latched by comparator 338 the first time that the second derivative waveform 404, as illustrated in FIG. 4D, goes negative (i.e., achieves a null value) after a sensed R-wave 406. In this case, a short delay 330 in the pressure signal path balances the electronic delays in the two signal paths, keeping the timing synchronized.

[0058]   The RA systolic pressure 324 and RA diastolic pressure 320 may also be
          derived according to the present invention. For RA systolic pressure 324, the
          RV pressure signal 412 is provided to sample and hold circuit 346 which is
          triggered upon detection of a P-wave by P-wave detection circuit 316.
          Comparator 344 latches the first time that the first derivative of RV pressure
          signal has a local positive maximum following detection of a P-wave (*see* FIG.
          5C). For RA diastolic pressure 320, the RV pressure signal 412 is provided to
          sample and hold circuit 350 which, following a preprogrammed delay of
          approximately 100 ms is triggered upon detection of a P-wave by P-wave
          detection circuit 316. Sample and hold circuit 350 captures the RA diastolic
          pressure 320 following the ~100 ms delay when the first derivative of RV
          pressure signal transitions from a null value to a positive value following
          measurement of RA systolic pressure 324.

[0059]   From the above description of the present invention, it is apparent that
          numerous pressure measurements (and derivatives and integrals thereof) and
          combinations thereof as described herein can be advantageously utilized
          according to the present invention. For example, the present invention may
          utilize right atrial or right ventricular pressure (e.g., systolic, diastolic, mean,
          etc.) and rate-of-change of same, including maximum or minimum (dP/dt),
          ePAD pressure, PA systolic and PA diastolic pressure, among others.

[0060]   If required, measurement of atrial pressures can also be accomplished similarly
          to the RV pressure measurement techniques previously described, as follows.
          The right atrial (RA) systolic pressure 324, like PA systolic pressure 322, is
          latched by a sample and hold circuit 346. Unlike PA pressure measurements
          however, latching occurs the first time that the dP/dt waveform 402 passes
          through zero subsequent to detection of a P-wave 408 as depicted in FIG. 4A.
          The RA diastolic pressure 320 is determined in the preferred embodiment
          shown in FIG. 3 by latching the RV pressure 312 after a short time delay (e.g.,
          100 msec) before the RA systolic pressure 324 measurement of interest. This
          is accomplished by delaying the RV pressure signal 412 with a delay circuit 348,
          and then latching the delayed signal with a sample and hold circuit 350 upon
          detection of a p-wave 408.

[0061]   Turning now to Fig. 6, implantation of an IMD 14 occurs at step 600 on a given
          date and the attending physician, for one reason or another, may choose to
          delay programming of biventricular or CRT pacing and, instead programs the
          IMD 14 to an alternative mode 604. In most cases, however, the physician will
          program IMD to biventricular pacing 602 either at implant or post-implant prior to
          release from the hospital. At the time of programming biventricular pacing 602,
          the physician will be asked to program the desired frequency of pressure
          measurements at step 606. Continuous beat-for-beat measurement may be
          selected (at step 614) and according to this programming decision the pressure
          sensing circuit 11 (FIG. 3) measures developing cardiac pressure (and
          derivatives and/or integrals thereof) for every cardiac cycle. According to the
          present invention, the operative timing circuitry within the IMD 14 iteratively
          adjusts one or more of the pacing intervals at step 616 (e.g., A-A, A-V, V-A,
          SAV, PAV, V-V, etc.) on an essentially continuous basis. The changes to the
          pacing interval(s) as well as the resultant pressure measurement values 618 are
          stored in IMD memory. These stored intervals and pressure values, along with
          the time or dates the measurements were taken (and changes to the intervals)
          are thus available to the physician for review at next follow-up 620.

[0062]   If, however, the physician selects a periodic pressure measurement regime
          (e.g., hourly, daily, weekly, or monthly, etc.) at step 606, the IMD 14 will
          immediately begin measuring pressure at step 608 and will iteratively test
          various pacing intervals at step 610 and implement the optimal pacing intervals
          based on hemodynamic performance as revealed by the pressure
          measurements 610. The next iterative pressure measurement cycle will occur
          after a predetermined amount of time after a prior cycle, based on the period of
          time chosen by the physician at step 606. The pressure values (e.g., direct,
          mean, median, average, derivative and/or integral) from the periodic
          measurements and the values for a given set of pacing intervals, and the dates
          of any changes will be stored in device memory at step 612 and remain
          available for physician review at the next follow-up 620. Of course, while a LUT
          can be used to store the pacing interval set and corresponding hemodynamic
          data other computer readable storage medium may be used. For example, as

is known to those of skill in the art, serial access memory (SAM) buffers, random access memory (RAM) including dynamic and static variants thereof (DRAM, SRAM), and read only memory (ROM) also known as "firmware," and programmable and electrically erasable programmable variants thereof (PROM, EEPROM also known as "flash memory") and the like may be successfully used in practicing the present invention. In addition to storing data as just described (i.e., a pacing interval set and the resultant hemodynamic data), other physiologic information may also be stored. For example, a resting condition heart rate, activity of daily living (ADL) condition heart rate, a sleeping condition heart rate, an upper tracking rate (UTR) condition heart rate, a lower tracking rate (LTR) condition heart rate, and the like may be stored in conjunction with the other stored data. Thus, a technique for initializing hemodynamic optimization according to the present invention involves providing multi-chamber cardiac pacing therapy to a patient at each one of a set of desired heart rates and measuring the resultant pressure development (and derivatives and/or integrals thereof) and storing same for comparison.

[0063]   An information set of pacing intervals, heart rate and resulting hemodynamic metrics can be used in at least two ways. First, the set can be used in the event that a chronically-implanted pressure sensor and/or pressure sensing circuitry fails to provide a useful signal, drifts from a previously calibrated condition, is removed, or is otherwise unavailable. In such event, until such time as useful pressure sensor signals later become available or a clinical intervention can be convenient scheduled, the paced heart rate(s) can control which set of pacing intervals - that corresponding to the best hemodynamic response - are used for given heart rate(s). Second (and somewhat related to the first way), a discrete heart rate or heart rate range(s) may be used as a controlling variable for delivery of the pacing stimulation therapy with "confirmatory reference" to the then-presently measured pressure values. In this second situation, periodic comparison of a stored information set with current pressure measurements are used to confirm that the patient's hemodynamics are responding as previously measured. If a material deviation is found to exist between the stored information and the current hemodynamic response, a new iteration of pacing

intervals could be performed and new hemodynamic responses recorded as previously described. In addition, the patient and/or the attending clinician may be notified, also as previously described. Of course, a significant decompensation event indicative of further deleterious cardiac remodeling in a heart failure patient could indicate an imminent heart failure hospitalization (HFH) event for the patient.

[0064]   Referring now to Figure 7, the reader can appreciate that an optimal AV delay was determined as 190 ms (PAV interval) and 140 ms (SAV interval) using the lowest obtained ePAD from the IHM as the criterion. At the optimal AV-interval the mean ePAD was 4.2 mmHg lower (31.9 mmHg) compared to the poorest setting (36.1 mmHg at 110 ms). The same PAV interval of 190 ms was determined optimal by the Echo-Doppler measurements.

[0065]   Referring now to the table set forth as Figure 8, during the acute test of various HR an increase in right ventricular pulse pressure (RVPP) and a decrease in right ventricular diastolic pressure (RVDP) and ePAD was seen when heart rate was programmed to 90 bpm.

[0066]   However, as depicted in Figure 9, in an ambulatory setting, a hemodynamic deterioration was indicated by increased ePAD and RVDP and decreased pulse pressure (PP) and dP/dt when HR was programmed above 70 bpm.

[0067]   The present patent disclosure demonstrates that continuous hemodynamic monitoring can be used to identify the optimal AV-delay in a pacemaker patient suffering from end-stage heart failure. The AV-delay determines the timing of late diastolic filling in relation to the onset of ventricular contraction and the duration of diastolic filling. An optimal tuning of the AV-delay improves left ventricular filling pressures in patients with a DDD-programmed pacemaker and is particularly important in the presence of a compromised left ventricular function. Therefore, we used the lowest ePAD pressure, an indirect parameter of the left ventricular end-diastolic pressure, as an indicator for the optimal AV interval.

[0068]   Importantly, measurements of the ePAD revealed the same optimal AV-delay as echocardiographic assessment of left ventricular diastolic filling by the standard Ritter method. The HR determined as optimal during the acute hemodynamic

test did *not* turn out to be optimal during performance of ADL in this patient. In the acute test a decrease of ePAD and RVDP was seen simultaneously with an increase of RVPP and maximal dP/dt at a heart rate of 90 bpm.

[0069]   While ambulatory (i.e., performing ADL), a HR programmed above 70 bpm had the opposite effect. That is, increases in ePAD and RVDP and lowering of RVPP and lowering of maximal dP/dt. This indicates that an "optimal" HR as determined by a test protocol in a resting patient may help to acutely improve hemodynamics, for example in the situation of acutely de-compensated heart failure patient where an increase in HR is required to improve cardiac output (CO).

[0070]   In stark contrast, however, the inventors have discovered that optimal ambulatory heart rates may only be determined during exercise or even better, while the patient performs ordinary, daily activities (i.e., ADL).

[0071]   In addition, the hemodynamic impact of different VV-delays (i.e., the interval between stimulation of the right and left ventricle), and the importance of different pacing modes (for example biventricular vs. left ventricular pacing) warrants further investigation.

[0072]   In this patient two devices were used. The IHM was implanted first as a part of a clinical multicenter study and the biventricular pacemaker was implanted second per clinical indications.

[0073]   Accordingly, a hemodynamic sensor integrated with (or within) a biventricular pacemaker or an ICD may be implemented according to the present invention as an integrated heart failure management device. Such a device allows for recording both long-term hemodynamic trends of a patient that will help improve overall treatment of the patient, as well as for the customized hemodynamic tuning of the pacemaker/ICD operational parameters on a patient-by-patient basis.

[0074]   In contrast to echocardiography, such a sensor-based optimization procedure may be performed by the pacemaker physician at any time and in the presence of a remote monitoring system even with the patient at home. Toward that end, the various data telemetry and remote patient management technologies of

Medtronic, Inc. may be readily applied so that such optimization can be simply, efficiently and quickly administered irrespective of patient location.

[0075]   In addition, an integrated hemodynamic sensor enables optimization of pacemaker algorithms according to the hemodynamic response during stress and during performance of the ADL. In addition, such an integrated hemodynamic sensor provides for short-term adjustments after changes of the patient's clinical condition.

[0076]   The present invention demonstrates that continuous hemodynamic monitoring provides useful information for the optimization of hemodynamicly important pacemaker algorithms such as the AV-delay, heart rate and pacing mode. In contrast to echocardiography, hemodynamic monitoring offers the potential to adjust pacemaker parameters even under the condition of exercise or during daily living. In patients with heart failure, the hemodynamic information may also be used to guide drug treatment and volume management. Therefore, future devices designed for the use in patients with heart failure, such as traditional dual chamber pacemakers, bi-ventricular resynchronization devices, ICDs, and the like may contain a hemodynamic monitoring sensor, constituting an integrated heart failure management device.

[0077]   While the present invention has been described with respect to a single patient and using only one illustrative embodiment, those of skill in the art to which the invention is directed will readily recognize that other related embodiments are taught hereby. The present invention is intended to cover all such embodiments as further set forth in the appended claims.